HIGH BLOOD PRESSURE

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PREFACE

Twelve years have elapsed since the first edition of this book. That set out to be comprehensive and to bring the important facts together in some relatively novel propositions. So much has subsequently been written that in this edition I have omitted much of the history included in the first edition, and have had to be selective in choosing new matter. To be truly comprehensive nowadays is to be tedious and dull.

The new data have on the whole confirmed, illustrated and amplified the new ideas put forward twelve years ago. No-one nowadays defends a dividing line between normotension and hypertension, though, regretfully, most are intellectually lazy enough to use it. Few deny that the malignant phase can be reversed by reducing arterial pressure. The results of treatment in both the benign and malignant phases have revealed a striking change in the causes of death, a change that is readily explained on the hypothesis here outlined.

Perhaps the most revolutionary change in knowledge and outlook has been in vascular disease. It is now clear that there are three common diseases associated with hypertension. These three are quite different in nature, pathogenesis and their relationship to raised arterial pressure. They are: (1) Fibrinoid necrosis, the *sine qua non* of the malignant phase, in which a grossly raised arterial pressure is decisive; (2) the miliary aneurysms of the cerebral arteries described by Charcot and Bouchard, the commonest cause of cerebral haemorrhage, in which raised arterial pressure and age are the major factors; (3) atheroma or nodular arteriosclerosis, an occlusive disease of large arteries, the cause of myocardial and cerebral infarction, probably a thrombotic disease, in which age, sex, serum cholesterol, cigarette-smoking, diet and exercise are factors that rank comparably with arterial pressure.

It is now possible to identify the complications of high arterial pressure as consequences of it. In some the arterial pressure plays the chief part; in others it is less important than other factors. But in all cases it is not a question of normotension or hypertension, it is the actual pressure that counts.

The present state of knowledge as set out in this volume is such that the physician can attain a reasonable understanding of the phenomena presented by the patient with raised arterial pressure. That understanding should enable him to predict and treat with a considerable degree of precision the patients who consult him.

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This new edition could never have been prepared had I not had the privilege of being Visiting Professor in the Department of Physiology, Dartmouth College, New Hampshire, for six months in 1966. I would like to express my gratitude to Dr Marsh Tenney, chairman of the department, and to the President and Trustees of Dartmouth College. The manuscript was put into its final state at the Villa Serbelloni, Bellagio, where I was the guest of the Rockefeller Foundation.

The references have again been checked, both in the text and in the bibliography, by Miss W. Gallagher, Librarian to St Mary's Hospital Medical School. She has also corrected numerous errors in the text. The reader will be as grateful as I am for her meticulous work. My wife read the manuscript through in its entirety, and made numerous improvements in style and lucidity. The galley proofs were read by Professor W. I. Cranston and Dr B. Juel-Jensen, who made many constructive and helpful criticisms and suggestions. The page proofs were read by my daughter, Mrs Gillham, Dr S. Goldby and Dr R. Elkeles. I am most grateful for their careful work. Individual chapters were read by Professor P. Beeson, Drs. J. Ledingham, W. F. Cook, P. Sleight and T. G. Pickering. They all made suggestions for improvement for which I am grateful. Finally, the hard work on the manuscript was done by my secretaries, Miss Anne Smallwood, Miss Angela Theed and Miss Sheila Hatton. They bore the brunt of the preparation of this book and have my corresponding gratitude. Finally, I am greatly indebted to Mr. A. S. Knightley of Messrs. Churchill for the care and patience which he has devoted to putting this book through the press.

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Chapter 1

INTRODUCTION

Twelve years ago, when the first edition of this book was published, the introduction was devoted to some difficulties which beset the problem of high blood pressure. It is a sign not a disease. It has a complex relation with vascular disease which is itself of more than one kind. Moreover, vascular disease is often symptomless until it is far advanced, as in the malignant phase of hypertension, cerebral haemorrhage, cerebral infarction, myocardial infarction or dissecting aneurysm.

These difficulties are inherent in the material. Much greater are the difficulties in the reader's mind. Some of these were evident 12 years ago. Others have become crystal clear since. Many of my great contemporaries have either not read what I have written, or, if they have, have not understood. They talk and write another language.

The controversy centres around high blood pressure without evident cause. The concept with which I was brought up, which most of my generation cling to, and which is consequently taught to the new generation, is that this is a disease of the familiar type characterized by a unique and specific fault of a qualitative nature. Those with the disease have the fault, those without do not. This is, in essence, the nature of the infectious diseases, the deficiency diseases, the diseases due to chemical agents, those transmitted by dominant and recessive genes; even the large group of cancers each have their specific histological abnormality. So it is supposed that there is a fundamental distinction between normotension and hypertension, that essential hypertension goes through a series of phases, prehypertension, intermittent hypertension, labile hypertension and fixed hypertension; and that these reflect the gradual unmasking of this specific fault which qualitatively distinguishes those with the disease from those without.

I spent the best 20 years of my life, from age 25 to 45, looking for this specific fault. Like others before and since I failed, and, perhaps unlike others, I began to wonder: had I failed because it wasn't there? Did the Holy Grail really exist? There was one piece of evidence, namely that the disease essential hypertension was transmitted by a single gene behaving as a Mendelian dominant. If this were true, then there must be a specific fault, which time, courage, ingenuity and a little bit of luck would display. So Hamilton, Sowry, Fraser Roberts and I set to work. But what was uncovered was not evidence for single gene inheritance, but evidence for graded, multifactorial or polygenic inheritance. Moreover, arterial pressure was distributed continuously in the population at large. The dividing line was nothing more than an artefact. Thus was I driven by the facts we had uncovered to look at the problem of essential hypertension from a new point of view. I saw arterial pressure for what it is, a quantity. I saw the consequences of raised

pressure as a number of different forms of breakdown of heart and vessels each with its peculiar set of causal factors, of which arterial pressure was one. The benign and malignant phases, the nature of whose difference I had discovered by chance, began to fall into place; the tragically speedy and uniform pattern of destruction in the malignant phase, the more tardy unpredictable course of the benign.

These views on the nature of essential hypertension which I had already formed 12 years ago have been fortified and sharpened by the new evidence that has been brought forward since. The insurance companies have amassed impressive data showing the quantitative relationship between arterial pressure and expectation of life, even at the lower levels of pressure. These data have displayed the huge difference between heart disease and vascular disease of the central nervous system in their quantitative relationships with arterial pressure. Miall and Oldham's beautiful population surveys have greatly increased our understanding of the role of inheritance and environment in determining arterial pressure. The controversy with my friend Robert Platt displayed the two sides and stimulated interest and new work. The different arterial diseases associated with ageing and high arterial pressure have begun to be sorted out and defined, though all too many writers fail to understand that what they call "hardening through the agency of porridge" (atherosclerosis) is as ill-assorted a hotch-potch as its name implies. That atheroma probably is a thrombotic disease and that platelets are the key to the thrombi is now emerging with increasing clarity. But the most important event in this field is Ross-Russell's rediscovery of Charcot and Bouchard's miliary aneurysms of the cerebral vessels and their relation to cerebral haemorrhage.

Another process of great importance has also been going on, the introduction of new and better drugs for reducing arterial pressure to levels chosen by the physician. There is now impressive evidence that malignant hypertension is indeed reversible by lowering arterial pressure, the most cogent piece of evidence for the quantitative view—indeed, incompatible with any other. And it is becoming clear that the prognosis of severe cases of benign hypertension can be improved by such treatment. Even more interesting is the fact that the frequency of the different modes of dying is being altered. Evidence for these statements comes particularly from Page and Dustan of Cleveland, Schroeder and Perry of St Louis, Sokolow of San Francisco, Brest and Moyer of Philadelphia, Leishman, McMichael and Hamilton's clinics in Britain, Smirk of New Zealand, Hood of Sweden, to name only a few. Substantially these workers agree, and our experience agrees with theirs.

The Concept

The story which becomes unfolded in this book is briefly as follows. Arterial pressure is a quantity—a biological quantity rather than a physical or chemical one—and susceptible to analysis by the standard methods of biometry. Physiologically speaking it is not a fundamentally important quantity like capillary pressure; it belongs, as it were, to the second rank. It is regulated by a variety of interdependent co-ordinated mechanisms,

ionic, hormonal, proprioceptive reflexes from the vascular system, locally acting substances and the state of the central nervous system. Here the greatest recent advance is the recognition of the profoundly different effects on arterial pressure of the sleeping and the waking brain.

Arterial pressure becomes raised in a number of specific diseases characterized by anatomical and chemical lesions; in acute and chronic nephritis, the collagen diseases and polycystic kidneys the anatomical lesion is described but the mechanism is unknown; in renal artery stenosis and coarctation of the aorta the mechanism is suspected and unproven; in Cushing's syndrome, Conn's syndrome and phaeochromocytoma in which the specific chemical fault is probable or proven. Chronic pyelonephritis remains somewhat inscrutable. But when these, and less common conditions are excluded there remains a large residue in which no specific lesion can be found—hyperpiesis, primary hypertension, essential hypertension, high blood pressure without evident cause.

These several diseases have their own characters which derive from their basic lesions, or absence of them. But when those are taken into account, the high blood pressure has concomitants or consequences—and the evidence from therapy now convicts them as consequences—that are common to all, allowing for age and sex. In all, the course may be that contrasted by Volhard and Fahr as the malignant 'bösartige' or bad course, or the benign 'gutartige' or good course. And, as has been noted, if the arterial pressure is reduced by any means whatsoever, the malignant course is reversed, the benign stayed and its pattern altered. How do we explain all this?

The key is, I think, elementary; arterial pressure is a quantity and its adverse effects are related numerically to it. This is, I fear, a basic platitude, but such is the divorce of medicine and science, that I have to go on uttering it.

One other basic platitude must be mentioned. In living creatures no single factor operates in isolation. It is always one of several, and in relation to others its effects vary from decisive, a 'limiting factor', to trivial. It would be scientifically naïve to suppose that any of its consequences arise from the arterial pressure alone. And since its consequences on heart and arteries take many different and definable forms it would be equally naïve to suppose it was of equal weight in all. This is what, as biological scientists, we should expect and what, as medical scientists, we find.

Looked at from this quantitative point of view we find the clinical manifestations of raised arterial pressure form a series ranging from those in which hypertension is severe and plays a chief part, to those in which it is mild or moderate and plays a comparatively small part. At one end of the series we find the phenomena of the malignant phase in which fibrinoid arteriolar necrosis is the outstanding lesion. These occur at any age from early childhood to late middle age; they occur in both sexes; they occur in primary and secondary hypertension provided only that it is severe. They are arrested and the tragic decline prevented by reducing pressure. In the same category is left ventricular failure when raised arterial pressure is its only cause. Next and intermediate are two manifestations in which age plays

an increasing role, heart failure and the Charcot Bouchard miliary aneurysms of the small cerebral arteries. At the other end of the series are diseases that occur with increasing age and with pressures that are not particularly high, but are commoner the higher the pressure. Atheroma or nodular arteriosclerosis is the commonest; in its aetiology maleness is a dominant factor while cigarette smoking and a disturbance associated with raised plasma cholesterol are others; this is the cause of myocardial infarction and other forms of coronary artery disease and the chief cause of cerebral infarction. In the same category are dissecting aneurysm of the aorta, saccular aneurysms of the aorta and the aneurysms of the Circle of Willis. Together these account for the varied pattern of the benign phase. When pressure is lowered by treatment left ventricular failure and heart failure disappear, the remaining lesions in which arterial pressure is a small factor become more obtrusive.

What causes the rise of pressure in essential hypertension? We do not know precisely. Certainly no specific fault has been identified and I personally am doubtful if one exists. But going further back we can assign roles to inheritance, which influences pressure at any age, and environment, which influences the rate of rise with age. And this is natural because, in one way at least, ageing represents a cumulative effect of environmental influences. The part played by the various factors naturally varies from one individual to another. One other point is important, and this was emphasized, I believe, for the first time in 1953. There is now abundant evidence that if by reason of a specific fault arterial pressure has been raised for a long time, removing the fault may not lower the pressure. The circulation has become adapted to its new state; it has, as it were, developed a bad habit; though what constitutes this adaptation still eludes us. It is of great interest to find that when arterial pressure has been kept at a lower level for long periods with drugs, then stopping the drugs in a few cases is not followed by a return of high pressure.

Such is the outline of what seemed a new concept of the nature of essential hypertension, when it was developed 12 years ago, and its subsequent expansion in the light of new data. In essence, it sees arterial pressure as a quantity and the consequences numerically related to the size of that quantity. The 'disease' essential hypertension, representing the consequences of raised pressure without evident cause, is thus a type of disease not hitherto recognized in medicine in which the defect is one of degree not of kind, quantitative not qualitative.

The Critics

The hypothesis just outlined has been greeted by medical scientists 'as a glimpse into the obvious', and by physicians as 'dangerous nonsense because it is against accepted teaching'.* It is apparently difficult for doctors to understand because it is a departure from the ordinary process of binary thought to which they are brought up. Is it normal or abnormal, physiological or pathological, health or disease, good or bad? Quantity is not an

*A criticism voiced by an eminent Russian at the Prague conference 1960. I treasure it—as from one revolutionary to another.

idea that is as yet allowed to intrude. Medicine in its present state can count up to two but not beyond.

Those who disagree with me think and talk in these qualitative terms. They talk, write and think in terms of 'hypertension' and 'normotension'. They envisage the disease developing in relation to an imaginary dividing line, 'prehypertension', 'intermittent hypertension', 'labile hypertension', 'fixed hypertension', being successive stages. Arterial pressure is thus expressed in terms of the dividing line instead of in mm Hg. This habit, which I find in the next generation as well as my own, is a vivid illustration of what Wilfred Trotter termed 'the mysterious viability of the false'.

One important point must be made crystal clear. If by disease one means those lesions that kill or maim, then high blood pressure is not the disease, any more than a raised serum uric acid is gout. The disease itself has been expressed as hypertensive disease or hypertensive vascular disease. The evidence now shows clearly that the changes in heart and blood vessels that kill or maim patients with high blood pressure are not all of one kind. Each kind is related quantitatively to arterial pressure, and in this relationship arterial pressure is a causal factor. But the numerical relationship, the coefficient of resemblance, is different in the several lesions. This is most clearly displayed by the data of the insurance companies, and by the effects of blood pressure reduction on the causes of death. Thus 'hypertensive disease' when fully analysed is an assembly of lesions of heart and vessels having a variety of causes, one of which is arterial pressure. Cause, arterial pressure, and effects, the maladies of heart and vessels, are related quantitatively.

Chapter 2

MEASUREMENT OF ARTERIAL PRESSURE

Arterial pressure in man may be measured in two ways; directly by inserting a hollow tube into a large artery and connecting this to an accurate pressure recording system, or indirectly by deflating a cuff of suitable size on the upper arm until the pulse wave first passes through (systolic pressure) and then achieves its maximum excursion (diastolic pressure).

The choice of method will depend on purpose. If the arterial pressure is to be measured in order to compare with other *physiological parameters*, then the *direct* method stands alone. If the pressure is to be measured *in the clinic* for diagnosis, prognosis or, to a lesser extent, management of the sick, then the *indirect* method again stands alone, and requires certain safeguards. For *epidemiological purposes*, the *indirect* method again stands alone, but requires other safeguards. Finally, for improved understanding of the behaviour and natural history of arterial pressure, and for more accurate treatment of those with high pressure, *automatic registration* over periods of 24 hours or longer may be needed.

THE DIRECT METHOD

Accurate measurement of arterial pressure demands that the lumen of the artery shall be connected to a manometer, of high frequency and small displacement, by a hollow tube whose properties shall not distort the cyclic pressure change. The more accurate records have been got by using wide needles in arteries, short wide rigid tubing, and high frequency, small displacement manometers. Less accurate readings are got more conveniently by using small, flexible nylon catheters inserted into the artery and connected to a strain gauge.

Manometers

The following have been used:

Optical. Frank, in 1903, laid down the principles which should govern the construction of a suitable manometer, particularly high frequency response and small displacement of moving parts. He devised a segment capsule in which the movements of a tightly stretched rubber diaphragm were recorded optically by a small plane mirror attached to one side. This was developed by Wiggers (1923), by Broemser (1928) who used a thin glass membrane, and by Hamilton (Hamilton, Brewer and Brotman, 1934) who used a thin metal diaphragm. This is now rarely used because electrical recording equipment is much more convenient than optical.

The variable capacitance manometer, in which a thin but stiff metal diaphragm forms one part of a minute condenser (Lilly, 1942; Tybjerg-Hansen and Warburg, 1947).

Variable inductance manometer. The manometer consists of a membrane (e.g. plastic) carrying an iron cylinder on one side which moves in a fixed magnetic field; movement changes the inductance. This manometer can be made very insensitive to lateral or rotating movement and very small. It can thus be used on the tip of a cardiac catheter (Gauer and Gienapp, 1950).

Resistance wire strain gauge, in which the manometer membrane stretches a wire and increases its electrical resistance. The wire forms one arm, or two arms, of a Wheatstone bridge. Strain gauge manometers often called blood pressure transducers, can now be obtained commercially of such sensitivity and small size that they may be used on the end of a cardiac catheter or stitched into a ventricle of the heart or artery and left there for considerable periods.

Tybjerg-Hansen (1949) defines the following properties of a good system:

(1) The catheter and all parts connected to the arterial lumen are easy to sterilize;
(2) Trapped air bubbles must be visible and removable;
(3) High natural frequency;
(4) High stability;
(5) Linear calibration;
(6) Insensitivity to temperature;
(7) Insensitivity to movement of manometer;
(8) Of low displacement, and therefore useable with long leads.

A full discussion will be found in Franke (1966).

INDIRECT METHOD OF MEASURING ARTERIAL PRESSURE IN MAN

The history of the evolution of indirect measurement of arterial pressure in man was given in the first edition and will not be repeated. Suffice it to say that the standard method is that of Riva-Rocci, as modified by von Recklinghausen (1901, 1906, 1930), who recommended a cuff 13 cm wide and 30 cm long as the most suitable. In this well-known method, a soft rubber cuff in a more rigid cloth case is applied to the upper arm and inflated to a pressure which obliterates the pulse; the pressure is allowed to fall until the pulse returns. The pressure is measured by a mercury manometer. The auscultatory method, now generally used, is based on the work of Korotkoff (1905), who described the sounds heard over the brachial artery immediately distal to the cuff. The Korotkoff sounds are:

Phase I	Sudden appearance of a clear, but often faint, tapping sound growing louder.
Phase II	The sounds are prolonged into a murmur.
Phase III	The sounds become clearer and increase in intensity.
Phase IV	The sounds quickly decrease in intensity and finally disappear.

In measuring the pressure, the cuff should be applied evenly and firmly to the bare upper arm, so that the lower edge is fully 2 cm above the crease of the elbow. The brachial artery is palpated with the arm stretched out fully

and the hand supinated, and the stethoscope placed over the artery. The cuff is inflated rapidly to some 50 mm Hg above the point when sounds cease, and the pressure then allowed to fall, the fall being regulated to not more than 2 mm per pulse beat at expected appearance of sounds, this rate being continued until sounds abruptly start to diminish (D_4) and finally disappear (D_5). The first appearance gives systolic pressure, the points of abrupt diminution and final disappearance are the rival claimants for diastolic pressure. The physician should be aware of three important phenomena. The first is the auscultatory gap. As the pressure is reduced during phase I, the sounds become fainter and disappear, to reappear again some millimetres lower. This phenomenon has been studied by Ragan and Bordley (1941), and appears to be influenced by the rate of inflation and deflation of the cuff and thus by the residual pressure in the vessels distal to the cuff after arresting the circulation. The importance of this phenomenon is that the cuff must be inflated well above systolic pressure if a false reading of systolic pressure is to be avoided. The second phenomenon occurs in aortic regurgitation, arterio-venous fistula and other conditions associated with a water-hammer, Corrigan or 'collapsing' pulse, and therefore with a large pulse pressure. In such circumstances, there may be no clear separation between phases III and IV, and a loud sound is audible over the brachial artery, even though the cuff pressure is zero. This is the well-known pistol shot sound of Duroziez, and is probably produced by the deformation of the artery by the stethoscope itself. Under such circumstances, the diastolic pressure and the transition from phase III to phase IV cannot be defined. The third is pulsus alternans. After the first sounds are heard, and as the pressure is reduced, the rate abruptly doubles, strong sounds alternating with weak sounds. This is diagnostic of left ventricular failure (see p. 354) and is therefore clinically of great significance. The pressure fall from the first appearance of the strong to the first appearance of the weak beats is a gauge of the degree of left ventricular failure. In pulsus alternans, the interval between strong and weak beats is the same. It is to be distinguished from pulsus bigeminus, as in regular extrasystoles (slow) or auricular flutter (fast), in which the intervals are alternately short and long.

The cuff should, according to theory and practice, be long enough to encircle the arm. Von Recklinghausen's work indicated a standard cuff of 13 × 30 cm. Unfortunately commercial instrument makers supply smaller cuffs. This is the commonest source of error in recording, particularly in the obese, today. The cuff should be at mid-chest level.

The manometer should be upright when the pressure is being read. The mercury should be at zero before the pressure in the cuff is raised. The mercury should be clean. The mercury should fall freely when the pressure is reduced. All of these manometric defects are not uncommon sources of error, particularly when communal instruments (as in wards or outpatient departments) are in use. A common and little-known error is blocking by dust of the pin-hole connecting the mercury column to the atmosphere; the pressure recorded by the manometer lags behind that in the cuff, giving erroneously high readings.

As will be seen in the next section, provided the precautions mentioned are taken, the indirect method gives a fair value for systolic. The evidence is controversial as to whether abrupt fading of the sounds (D_4) or cessation of sounds (D_5) is the best estimate of diastolic. In all the work from my laboratory the point of abrupt diminution has been taken as diastolic. A WHO Expert Committee (1962) recommends that both be recorded.

On the continent of Europe, the arterial pressure is frequently determined by an oscillometer, in which the cuff is connected to a high-frequency type of pressure gauge. One of the best known of these is Pachon's oscillometer (Pachon, 1909), now commonly used with Gallavardin's double cuff, an upper and a lower, connected to the two sides of a high-frequency diaphragm type of pressure gauge. The oscillations of the diaphragm record the volume change of the main artery of the limb transmitted to the air in the cuff.

Another type is Plesch's tonoscillometer (1930), in which two elastic manometers of different size are used respectively to record the pressure in the cuff and its pulsations. In both these types of apparatus, as in the earlier plethysmographs, the first pulsation occurring as the pressure is reduced is held to occur at systolic pressure, the maximum pulsation at diastolic pressure.

Comparison of Direct and Indirect Measurements of Arterial Pressure in Man

The first comparison of pressures measured by direct methods just described and indirect methods was by Wolf and v. Bonsdorff (1931). The pressure was measured directly from one brachial artery by inserting into it a needle connected through a saline-filled lead tube to Bröemser's glass membrane manometer recording optically. Blood pressures were measured from the other arm by the auscultatory method, and by Plesch's tonometer, before, during and after the direct measurement. The cuff size was not stated. They observed considerable differences between the pressures measured indirectly by both methods and the true values, and they considered that, while the indirect method gave a correct appreciation of the order of pressure, it was so inaccurate that small differences were of no significance.

In 1936 Hamilton, Woodbury and Harper compared the brachial artery pressure measured directly by the optical capsule and indirectly by the auscultatory method. The indirect measurements were on an average 3–4 mm too low for systolic and 9 mm too high for diastolic using 'fading of the fourth phase'. They concluded that their results indicated 'that the indirect method agrees reasonably well with the direct method'. In 1938 Woodbury, Robinow and Hamilton compared the pressure, measured directly, from the umbilical artery and from the brachial artery, measured indirectly by palpation, in infants at birth. The direct method gave higher readings than the indirect with a cuff 4–6 cm wide, but good agreement when a cuff 2–5 cm wide was used. They point out, however, that the form of the pulse wave in the umbilical artery differs from that in the brachial. In 1939 Robinow, Hamilton, Woodbury and Volpitto compared direct readings from the